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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM

Office Action Summary	Application No.	Applicant(s)	
	09/355,254	WAGNER ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,26,27 and 40-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,26,27,40-45,48,49,51-53,59,63,65 and 68-70* is/are rejected.

7)☒ Claim(s) *46,47,50,54-58,60-62,64, 66 and 67* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12-11-03, 1-20-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 7-12-04.

Claims 24, 26, 27, 40-70 are pending in the instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Applicant's arguments, filed 7-12-04, with respect to the rejection(s)of claim(s) 24, 26, 27, 40-45, 48, 49, 51-53, 56, 59, 63, 65, 68 and 70 under 102 and 103 have been fully considered and are persuasive because the disclosure by Davis of the instantly claimed SEQ ID NO: 10 and relied upon in the 102 and 103 rejections of record does not predate the priority date awarded the instant application. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made under 103 which does not rely on the Davis reference.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24, 26, 27, 40-45, 48, 49, 51-53, 59, 63, 65 and 68-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chu et al, in view of the combined teachings of McKnight et al, Hinrichs et al, Dolganov et al, Stanford et al, Levy et al, Green et al, Ono et al, Cha et al and Harada et al, the combination further in view of Hutcherson et al.

The claims are drawn to a pharmaceutical composition comprising at least one polynucleotide sequence of a binding site for a transcription factor selected from the group consisting of SEQ ID NO: 8-13, 17, 19 or 21-23, and further comprising at least one antigen, a pharmaceutically acceptable carrier or diluent, which polynucleotide comprises at least one phosphorothioate internucleotide linkage.

Chu et al (J. Exp. Med. 186(10): 1623-1631, 1997) teach the induction of the immunological Th1 response in mice following co-administration of unmethylated CpG containing oligonucleotides in combination with an antigen (hen egg lysozyme). Chu et al also teach a correlation of expression of IL-4, -5, -10 and -13 with the elicitation of a

Th2 response, and expression of IL-12 and IFN-gamma with elicitation of a Th1 response. Chu et al increased susceptibility to infection or toxicity with the induction of the wrong response type (e.g. Th2 versus Th1), as well as the need to control the type of response induced for achieving treatment efficacy (see abstract and introduction on pages 1623-1624; text on pages 1628-1629). Chu et al teach the co-administration of an antigen and a CpG containing oligonucleotide for generating a Th1 type of immune response in order to induce increased vaccine efficacy, and Chu et al teach the Th1 type of immunity as a protective response to infections with certain microbes (text on page 1623).

Chu et al do not teach the particular polynucleotide sequences claimed, nor the incorporation of phosphorothioate internucleotide linkages into oligonucleotides.

McKnight et al (USPN 5, 591,825, Jan. 7, 1997) teach a pharmaceutical composition consisting of the polynucleotide sequence of SEQ ID NO: 21 and a pharmaceutically compatible diluent (e.g. water), whereby the polynucleotide comprises a binding site for a transcription factor of a cytokine (See especially the abstract, col. 10, claims 1-3, and SEQ ID NO: 3 of McKnight et al, and the sequence alignment data provided in the Office action mailed 7-25-03). McKnight et al also teach the role of IL-4 in expansion of Th2 T helper cell subsets over Th1, and the role of Th2 expansion in various immunological diseases (e.g. autoimmune conditions, allergies, inflammation) (see col. 1, lines 38-50). McKnight et al also teach a motivation to inhibit Il-4 expression, including by inhibiting transcription factors in binding to their targets,

thereby inhibiting Il-4 in its role in Th2 T helper cell expansion (see col. 1-2, col. 4, line 41-col. 6, line 47).

Hinrichs et al (USPN 5,641,486 June 24, 1997) teach a pharmaceutical composition comprising the polynucleotide sequence of SEQ ID NO: 8 and a pharmaceutically compatible diluent (e.g. water), whereby the polynucleotide comprises a binding site for a transcription factor of a cytokine (See especially the abstract and SEQ ID NO: 2 of Hinrichs et al and the sequence alignment data provided in the Office action mailed 7-25-03).

Dolganov et al (Blood 87(8): 3316-26, 1996) teach a pharmaceutical composition comprising the polynucleotide sequence of SEQ ID NO: 9 and a pharmaceutically compatible diluent (e.g. water), whereby the polynucleotide comprises a binding site for a transcription factor of a cytokine (See especially figure 2 on page 3319 and the sequence alignment data provided in the Office action mailed 7-25-03). Dolganov et al also teach the control of expression of various interleukins (e.g. IL- 4 and IL-13) by transcriptional activation elements, as well as teaching the role of various interleukins in the generation of immune responses, such as IgE isotype switching, and unwanted inflammatory responses associated with IL-4, IL-13 induction and IgE class switching (see the abstract and introduction on page 3316). Dolganov et al also teach a role of various cytokines in T-cell activation, and the expansion of functional memory T cells in response to a cognate antigen (see discussion, right hand column on page 3323-page 3324). Dolganov et al teach the significance of antigen exposure in generating an

enhanced immunoprotective response in an organism (text page 3323, right hand column).

Stanford et al (Immunogenetics 35: 408-11, 1992) teach a pharmaceutical composition comprising the polynucleotide sequence of SEQ ID NO: 17 (encoding the Ly-6A.2 gene) and a pharmaceutically compatible diluent (e.g. water), whereby the polynucleotide comprises a binding site for a transcription factor (See especially figure 2 on page 409, last two paragraphs on page 410, and the sequence alignment data provided in the Office action mailed 7-25-03). Stanford et al teach the physiologic role of the Ly-6A.2 gene in T cell activation (see first paragraph on page 408).

Levy et al (USPN 5,616,489, April 1, 1997) teach a pharmaceutical composition consisting of the polynucleotide sequence of SEQ ID NO: 19 and a pharmaceutically compatible diluent (e.g. water), whereby the polynucleotide comprises a binding site for a transcription factor of a cytokine (See especially the abstract and SEQ ID NO: 12 of Levy et al and the sequence alignment data provided in the Office action mailed 7-25-03).

Green et al (WO 96/17960, 13.06.1996) teach a pharmaceutical composition consisting of the polynucleotide sequence of SEQ ID NO: 13 and a pharmaceutically compatible diluent (e.g. water), whereby the polynucleotide comprises a binding site for a transcription factor of a cytokine (See especially the abstract, page 3, pages 13-18, Accession No. AAT32689 of Green et al and the sequence alignment data provided in the Office action mailed 7-25-03). Green et al also teach the inhibition of transcription

factor binding as a means of inhibiting hepatitis B viral transcription as antiviral therapy (see pages 2-3).

Ono et al (WO 96/12823, 02.05.1996) teach a pharmaceutical composition comprising the polynucleotide sequence of SEQ ID NO: 12 and a pharmaceutically compatible diluent (e.g. water), whereby the polynucleotide comprises a binding site for a transcription factor of a cytokine (See especially the abstract, example 4 on page 42, and Accession No. AAT18820 of Ono et al and the sequence alignment data provided in the Office action mailed 7-25-03). Ono et al also teach the role of MHC class II molecule dysregulation in immune disorders, and the critical role of expressing class II MHC molecules by antigen presenting cells in the process of endocytosing and processing foreign antigens. Ono et al teach the transcriptional inhibition of class II MHC molecules by inhibitory DNA-proteins (see pages 1-6).

Cha et al (J. Biol. Chem. 269(7): 5279-87, 1994) teach a pharmaceutical composition comprising the polynucleotide sequence of SEQ ID NO: 22 and a pharmaceutically compatible diluent (e.g. water), whereby the polynucleotide comprises a binding site for a transcription factor of a cytokine (See especially the figure 1 on page 5281, figure 3 on page 5282, Accession No. L24442 of Cha et al, and the sequence alignment data provided in the Office action mailed 7-25-03). Cha et al teach transcriptional regulatory elements that affect the expression of type 1 interferon genes (see pages 5279 and 5286).

Harada et al (USPN 5,834,188, Nov. 10, 1998) teach a pharmaceutical composition comprising the polynucleotide sequence of SEQ ID NO: 11 and a

pharmaceutically compatible diluent (e.g. water), whereby the polynucleotide comprises a binding site for a transcription factor of a cytokine (See especially the abstract, col. 2-5, col. 25-26, SEQ ID NO: 2 of Harada et al and the sequence alignment data provided in the Office action mailed 7-25-03).

Hutcherson et al (USPN 5,723,335, Mar. 3, 1998) teach the incorporation of a phosphorothioate internucleotide linkage into CpG containing oligonucleotides for stimulating a local immune response (see the abstract, col. 4-5; examples 1-12, col. 11-16, SEQ ID Nos: 20-22 and claims 1-3).

It would have been obvious to one of ordinary skill in the art to make pharmaceutical compositions comprising a CpG containing polynucleotide sequence, an antigen and a pharmaceutically compatible diluent because Chu et al teach the administration of these compositions for inducing a Th1 immune response. One of ordinary skill in the art would have been motivated to co-administer an antigen and a CpG containing oligonucleotide to an organism because Chu et al teach increased immune protection in an organism by co-administering an antigen and a CpG containing oligonucleotide and generating a Th1 immune response. Furthermore, Chu et al teach the induction of protective immunity to infection with certain microbes by generating a Th1 immune response in an organism by co-administering an antigen and a CpG containing oligonucleotide, and Dolganov et al teach the significance of antigen exposure in generating enhanced immunoprotective responses in an organism (page 3323, right hand column). One of ordinary skill in the art would have been motivated to administer an Th1 inducing composition comprising a CpG containing polynucleotide

sequence, an antigen and a pharmaceutically compatible diluent because it had been taught previously by Chu and others that a Th2 immunological response causes undesirable inflammatory side effects (e.g. involving induction of interleukins including IL-4, 5, 10 or 13) while a Th1 response instead causes a more desirable immune response involving indirect activation of macrophages and natural killer cells, and provides a safer protective response to infection with various microbes compared to a Th2 response (e.g. see Chu on page 1623). One of ordinary skill in the art therefore would have expected that the administration of the compositions claimed would provide a safer (Th1) immune response. It would have been obvious to one of ordinary skill in the art to include one of the CpG containing polynucleotides taught previously by McKnight et al, Hinrichs et al, Dolganov et al, Stanford et al, Levy et al, Green et al, Ono et al, Cha et al or Harada et al (SEQ ID NOS: 8, 9, 11-13, 17, 19 and 21-23) because these polynucleotides were known in the art, they comprise a CpG containing motif which induces a safer Th1 type immune response (as illustrated above and taught previously by Chu et al), and these polynucleotides further comprise sequences involved in the transcriptional regulation of various cytokines known to cause unwanted inflammatory side effects. One of ordinary skill in the art would have been motivated to include in the pharmaceutical compositions these sequences involved in the transcriptional regulation of various cytokines, either indirectly (as with MHC class II genes, type 1 interferon, or Hepatitis B virus) or directly (as with IL-4, IL-13) because the regulation of cytokine levels provides for the regulation of unwanted inflammatory side effects, as taught previously by Chu, McKnight, Green, Ono and Cha.

One of ordinary skill in the art would have been motivated to make these pharmaceutical compositions because the polynucleotide sequences comprising binding sites for transcription factors for cytokines, in combination with an antigen and a compatible diluent, provide for immunological modulation (including adjuvancy) in an organism, and the polynucleotide sequences claimed each comprise a CpG motif that had been taught previously to enhance immunomodulation, causing a shift from the undesirable Th2 to a Th1 response, with the corresponding shift away from induction of cytokines known to cause inflammatory side effects and IgE production, as taught previously by Chu, Dolganov and McKnight. One of ordinary skill in the art would have expected that the polynucleotides - taught previously by Hinrichs et al, Dolganov et al, Stanford et al, Levy et al, Green et al, Ono et al, Cha et al, Harada et al and McKnight et al, wherein each polynucleotide contains a transcriptional regulatory sequence effecting the expression of cytokines either indirectly or directly – would have enhanced immunomodulatory (Th1) effects because of the presence of CpG motifs, as well as the transcriptional regulatory sites regulating the induction of unwanted cytokines including Il-4, IL-13. One of ordinary skill in the art would have been motivated to make compositions comprising these polynucleotide sequences to enhance Th1 responses upon administration in an organism, as had been taught previously by Chu and others. One of ordinary skill in the art would have been motivated to incorporate phosphorothioate modifications into the polynucleotides because it had been taught previously in the art by Hutcherson that this internucleotide modification provides an enhanced localized immune response. One of ordinary skill in the art would have

expected that these compositions would provide enhanced immunoadjuvancy, and would enhance a Th1 related immune response, and minimize the induction of Th2 related cytokines following their administration. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

Claims 46, 47, 50, 54, 55, 56, 57, 58, 60-62, 64, 66 and 67 appear free of the prior art searched and of record. These claims are objected to because they depend from a rejected claim.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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JZ
8-11-04